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Date: March 28, 2006

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Our Docket No. TUF 101 CIP
Your Docket No.

Client/Matter No. 095169/00004

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MESSAGE:

PART 1 OF 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Saul Tzipori, Ramaswamy Balakrishnan and Arthur Donohue-Rolfe

Serial No.: 10/041,958 Art Unit: 1645

Filed: January 7, 2002 Examiner: Mark Navarro

For: *HUMAN NEUTRALIZING ANTIBODIES AGAINST HEMOLYTIC UREMIC SYNDROME*

Attachments:
Transmittal Form PTO/SB/21
Fee Transmittal Form PTO/SB/17
Substitute Appeal Brief
One (1) Reference
Three (3) Declarations
Copy of Decision in Related Appeal

{45065552.1}

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	70

Application Number	10/041,958
Filing Date	January 7, 2002
First Named Inventor	Saul Tzipori
Art Unit	1645
Examiner Name	Albert Mark Navarro
Attorney Docket Number	TUF 101 CIP

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
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- [ ] Petition to Convert to a Provisional Application
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- [ ] Terminal Disclaimer
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- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
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- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please identify below):

Three Declarations Under 37 C.F. R. 1.132; One (1) Reference; copy of Decision on Related Appeal

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Pabst Patent Group LLP		
Signature	Rivka D. Monheit		
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Date	March 28, 2006	Reg. No.	48,731

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Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2006

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 0.00

Complete if Known	
Application Number	10/041,958
Filing Date	January 7, 2002
First Named Inventor	Saul Tzipori
Examiner Name	Albert Mark Navarro
Art Unit	1645
Attorney Docket No.	TUF 101 CIP

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1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
11 - 20 or HP =	0	x	=

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
1 - 3 or HP =	0	x	=

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
- 100 =	/ 50 =	(round up to a whole number)	x	=

4. OTHER FEE(S)

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Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge):	

SUBMITTED BY

Signature	Rivka D. Monheit	Registration No. (Attorney/Agent) 48,731	Telephone 404-879-2152
Name (Print/Type)	Rivka D. Monheit		Date March 28, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Saul Tzipori, Ramaswamy Balakrishnan and Arthur Donohue-Rolfe			
Serial No.:	10/041,958	Art Unit:	1645	RECEIVED CENTRAL FAX CENTER
Filed:	January 7, 2002	Examiner:	Mark Navarro	MAR 2 8 2006

For: *HUMAN NEUTRALIZING ANTIBODIES AGAINST HEMOLYTIC UREMIC SYNDROME*

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Alexandria, VA 22313-1450

SUBSTITUTE APPEAL BRIEF

Sir:

In response to the notice of the Board of Patent Appeals and Interferences mailed on October 11, 2005, and the Notice mailed March 23, 2006, please substitute this Appeal Brief with the Appeal Brief submitted via facsimile on September 14, 2004 and on November 11, 2005. It is noted that it took the examiner four months to advise the undersigned of the alleged deficiency.

This is an appeal from the rejection of claims 26-36 in the Office Action mailed April 16, 2004, in the above-identified patent application. A Notice of Appeal with authorization to charge Deposit Account No. 50-3129 in the amount of $165.00, the fee for filing a Notice of Appeal for a small entity, was filed on July 16, 2004. The Commissioner was also authorized to charge the fee in the amount of $165.00 for a small

entity, for the filing of Appellants' Brief, to Deposit Account No. 50-3129 on September 14, 2004. It is believed that no additional fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Trustees of Tufts College, Medford, MA. This product is in clinical trials.

(2) RELATED APPEALS AND INTERFERENCES

There is a related appeal in Serial No: 10/230,614 filed August 29, 2002, which directly affects, which would be directly affected by, or which may have a bearing on the Board's decision in this appeal. A decision was rendered in this case on September 26, 2005. This application is a continuation-in-part of the application in the previous appeal.

(3) STATUS OF CLAIMS

Claims 26-36 are pending, rejected and on appeal. The text of each claim on appeal, as pending, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The pending claims were last amended by the Amendment mailed January 9, 2004, and entered upon filing of a Request for Continued Examination on February 4, 2004.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 26 defines a dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II *in vivo*, wherein the antibodies are specifically reactive with a single

subunit of the Shiga like toxin II produced by *Escherichia coli* which causes hemolytic uremic syndrome, to prevent or treat hemolytic uremic syndrome in a human (page 6, lines 15-16; page 7; page 34, lines 11-22); page 37, lines 3-12; page 38, line 12 to page 46, line 15).

Claim 27 defines the antibodies as human monoclonal antibodies (page 5, lines 12-19). Claim 28 defines the antibodies as produced by recombinant DNA methodology (page 5, lines 19-25). Claim 29 defines the antibodies as chimeric monoclonal antibodies (page 6, lines 1-4; page 15, lines 5-24).

Claim 30 restricts the claimed antibodies to antibodies which bind to the alpha subunit of the Shiga like toxin II (page 7, lines 10-15; page 18, line 9 to page 19, line 6; page 34, lines 11-22; page 38, line 12- page 46, line 15; page 47, lines 3-5).

Claim 33 restricts the claimed antibodies to antibodies which bind to the beta subunit of the Shiga like toxin II (page 7, lines 10-15; page 18, line 9 to page 19, line 6; page 34, lines 11-22; page 38, line 12- page 46, line 15).

Claim 31 defines the dosage formulation as being effective to prevent neurological signs of hemolytic uremic syndrome or lesions, wherein the neurological signs or lesions (page 36, lines 11-14) are selected from the group consisting of bloody diarrhea, acute renal failure (page 20, lines 10-14), cerebral hemorrhaging, bacterial shedding into feces, bacterial lesions, paddling, head-pressing, ataxia, convulsions and wasting (page 36, lines 16-20; page 42, lines 1-5). Claim 32 defines the dosage formulation wherein the antibodies are effective to prolong survival (page 40, lines 20-25; page 43, lines 13-25). Claim 34 defines the dosage formulation as equivalent to 4 ml serum from an animal immunized with Shiga-like toxin II/kg body weight (page 20, line

1). Claim 35 defines the dosage formulation as that which is effective to produce a serum level of anti-Shiga toxin II antibodies of at least 0.5 micrograms/ml (page 43, lines 8-12). Claim 36 defines the dosage formulation as that which is equivalent to a dosage of 3 mg human monoclonal antibody to Shiga-like toxin II administered to a newborn pig (page 36, lines 14-16).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented on appeal is whether claims 26-36 are obvious under 35 U.S.C. 103 over U.S. Patent No. 5,512,28 to Krivan *et al.* ("Krivan ") and Perera, et al., J. Clin.Microbiol. 26(10), 2127-2131 (1988) in view of WO 90/07861 by Queen *et al.* and Engelman *et al.*, Human Hybridomas and Monoclonal Antibodies, NY Plenum Press 1985 pp. 23-27 ("Engelman") and further in view of U.S. Patent No. 6,080,400 to Williams.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed in more detail below. There are a number of elements not disclosed by the prior art, in addition to the failure to provide the motivation to select and combine the elements as defined by the independent claims.

Claims 27-29 are drawn to the source of the monoclonal antibodies (claim 27, human; claim 28, recombinant DNA; claim 29, chimeric antibodies).

Claims 30 and 33 are specific to particular subunits of the Shiga like toxin II, subunit A and subunit B.

Claim 31 is drawn to a specific formulation for preventing the neurological signs of HUS - none of the prior art even recognizes this is an issue, much less provides guidance on what would be an effective amount to treat or prevent.

Claims 32, and 34- 36 relate to specific dosages. There is no art disclosing or suggesting the effective dosages.

(8) ARGUMENTS

(a) The Invention

Hemolytic uremic syndrome, or HUS, is a disorder marked by kidney failure, hemolytic anemia, thrombocytopenia (platelet deficiency), coagulation defects, and variable nervous system signs. This disorder is most common in children. It frequently occurs after a gastrointestinal (enteric) infection, often one caused by a specific *E. coli* bacteria (*Escherichia coli* O157:H7). It has also been associated with other enteric infections including Shigella and Salmonella and some non-enteric infections.

HUS, once relatively rare, is increasing in children. It is the most common cause of acute kidney failure in children. Several large outbreaks in 1992 and 1993 were attributed to undercooked hamburger contaminated with *E. coli*. Because of this association, supermarket hamburger has new labeling, and there are new temperature guidelines for hamburger cooked at fast-food chains and restaurants. HUS is less common in adults.

HUS is one of the most common causes of sudden, short-term kidney failure in children. In severe cases, this acute kidney failure may require several sessions of dialysis to take over the kidneys' job of filtering wastes from the blood, but most children recover without permanent damage to their health. Most cases of HUS occur after an infection of

the digestive system by *Escherichia coli* bacterium, which is found in contaminated foods like meat, dairy products, and juice. Some people have contracted HUS after swimming in pools or lakes contaminated with feces. The infection of the digestive tract is called gastroenteritis and may cause the child to vomit and have stomach cramps and bloody diarrhea. Most children who experience gastroenteritis recover fully in 2 or 3 days and do not develop HUS. In a few children, however, HUS develops when the bacteria lodged in the digestive system make toxins that enter the bloodstream and start to destroy red blood cells. Symptoms of HUS may not become apparent until a week after the digestive problems. The child remains pale, tired, and irritable. Other symptoms include small, unexplained bruises or bleeding from the nose or mouth that may occur because the toxins also destroy the platelets, cells that normally help clotting. Urine formation slows because the damaged red blood cells clog the tiny blood vessels in the kidneys, making them work harder to remove wastes and extra fluid from the blood. The body's inability to rid itself of excess fluid and wastes may in turn cause high blood pressure or swelling of the face, hands, feet, or the entire body. This progression to acute kidney failure occurs in about half the cases of HUS.

Bacteria such as *E. coli* vary tremendously in the hosts that they infect and which toxins they produce. Some strains primarily affect cattle, others pigs, still others humans. Results obtained using organisms isolated from humans will be different from results obtained from organisms isolated from cattle or pigs. This is an extremely important point. As is clear from the examples in the specification, there is tremendous variation among *E. coli* that cause disease. The *E. coli* that causes disease in children is not the same *E. coli* that causes disease in calves. In calves, the disease is typically characterized

by scours - diarrhea, and is most common in dairy calves that are bottle fed. Most farmers do not treat animals by i.v. injection, but prefer to add treatment to the bottles - hence the emphasis in the prior art on enteral treatments for cattle. However, the reason these *E. coli* infect calves and not people is because the bacteria cannot infect an animal unless they attach to receptors on the gut lining, and the receptors are species specific. This is explained in the declarations discussed in more detail below. Because the receptors are specific to a particular species, one cannot extrapolate from studies in most animals to efficacy or treatments in humans. Only one animal model, discussed below, a newborn piglet which is deprived of colostrums, can be used as a model for bacteria which infect human, because the bacteria which infect mice, rats, and cows will not bind to the receptors in the human gastrointestinal tract - and *vice versa*.

Only recently has it been known which of the many toxins produced by the various bacteria cause the most serious illness. This is in part due to the lack of an appropriate animal model, discussed below, which could be used to compare the effects of the different toxins, and antibodies specific to the different toxins. Appellants were the first to discover that of the two major toxins produced by *E. coli* implicated in HUS in humans, Shiga-like toxin I and Shiga-like toxin II, it is the latter, Shiga-like toxin II, that causes the worst symptoms of HUS, leading to kidney failure and death. This is important since one can screen bacteria to see which toxins, and in which amounts, are produced. As demonstrated by the examples in appellants' specification, bacteria which produce Shiga-like toxin I ("stx1 "), or a mixture of Shiga-like toxin II ("stx2"), are not as deadly as strains that produce primarily Shiga-like toxin II. However, the studies also show that one can administer antibodies directed to the Shiga-like toxin II, rather than a

mixture of antibodies, and selectively prevent the worst symptoms of the disease. Since treatment is primarily supportive, the patients will then recover without the permanent kidney damage and other long term side-effects of the disease.

Appellants have developed a dosage formulation to prevent or treat hemolytic uremic syndrome in a human individual exposed to or infected by *Escherichia coli* producing Shiga-like toxin II, which can be administered by administering intradermally, subcutaneously, intravenously, or intramuscularly, to an individual presenting with bloody diarrhea, diagnosed with infection by *Escherichia coli* producing Shiga-like toxin II, or exposed to an individual infected with or exposed to the same source of infection with *Escherichia coli* producing Shiga-like toxin II, comprising an effective amount of monoclonal human or humanized antibodies consisting of antibodies reactive with a single subunit of Stx2, which neutralize Stx2, to prevent or treat hemolytic uremic syndrome in a human (page 5, line 4-page 6, line 11; page 7, lines 10-22; claim 26). In the preferred embodiment, the monoclonal antibodies are human monoclonal antibodies or produced by recombinant DNA methodology, for example, chimeric monoclonal antibodies (page 12, line 18, to page 15, line 24; examples; claims 27-29).

In one embodiment, the antibodies are administered when the individual presents with bloody diarrhea (page 8, line 25, to page 9, line 4). Alternatively, the antibodies are administered to the individual prior to the onset of symptoms (page 8, lines 16-24, such as bloody diarrhea, cerebral hemorrhage, seizures, or kidney damage. In other embodiments, the antibodies are administered when the individual is diagnosed with *E. coli* infection, or at the onset of hemolytic uremic syndrome (page 20, lines 5-16).

The claims in this appeal are specific to the dosage formulation per se, and are drawn to antibodies to specific subunits (page 7, lines 10-18; pages 16-60, especially pages 44-45; claims 30 and 33) and specific dosages (claims 34-36) which could be determined only by the use of an animal model that was actually predictive of human infection (the neonatal pig) using bacterial strains obtained from humans with severe disease that at least in some cases was fatal (examples at pages 16-60).

It must be emphasized that the data in the application was essential for one of skill in the art to know that antibodies to a Stx2 IN HUMANS would be effective in treating or preventing HUS, that antibodies to a SINGLE SUBUNIT of Stx2 IN HUMANS would be effective in treating or preventing HUS, and what kind of actual DOSAGES would be useful.

The examiner's rejections are all premised on whether or not one skilled in the art could predict, with a reasonable expectation of success, that which is claimed, from prior art that provides no data whatsoever with respect to *E. coli* infection IN HUMANS. Due to the unique nature of this disease, which leads to HUS, once simply cannot do this. This is why multiple declarations were submitted in response to the rejections, showing that independent, unpaid third parties all of whom are above ordinary skill in the art, felt that one must have a model predictive of success in HUMANS, and actual data, to reach that which is claimed.

This technology is very important. It is currently being developed using non-profit research funds due to the critical need for such a product, a need which has been known for many years but for which there is still no accepted product available to clinicians. This is yet further evidence of the non-obviousness of this product.

(b) Rejection Under 35 U.S.C. § 103

Claims 26-36 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,512,282 to Krivan *et al.* ("Krivan") and Perera *et al.* J. Clin. Microbiol. 26(10):2127-2131 (1988) ("Perera") in view of WO 90/07861 by Protein Design Labs, Inc ("Queen") and Engelman *et al.* "Human Hybridomas and Monoclonal Antibodies ed. Engleman, Foung, Larrick, Raubitschek (Plenum Press 1985) pp. 95-112 ("Engelman") and further in view of U.S. Patent No. 6,080,400 to Williams.

None of the prior art teaches one skilled in the art to use an antibody to only a single subunit of the Stx2 for treatment or prevention of disease. None of the prior art recognizes that one only has to block Stx2 IN HUMANS to prevent the mortality and other extremely serious complications of HUS associated with certain highly virulent strains of *E. coli*. None of the prior art recognizes that the toxins associated with strains of *E. coli* that infect humans, as compared to other animals, are different, and that antibodies to toxin from animal strains may not be effective in treating or preventing complications of HUS. None of the prior art recognizes that one can block only a single subunit and still treat or prevent the high mortality or serious complications of HUS. Without recognizing these aspects, and identifying a useful animal model, one cannot predict an effective dosage, much less the dosage ranges defined by the dependent claims.

As discussed in more detail below, the art recognizes that antibodies should be useful in the treatment of HUS (Krivan, Williams). The art recognizes that one can make antibodies to just one subunit (Perera) which are useful in diagnostics. There is nothing that would lead one to substitute these subunit specific antibodies into Krivan, determine

an effective dosage, and then have a reasonable expectation of success. None of the art demonstrates any successful treatment or prevention of clinical symptoms.

Therefore one skilled in the art would not be lead either to select antibodies as defined by all claims now pending, not just claim 30 as previously presented, nor to have a reasonable expectation of success if one did so.

i. The Legal Standard for Obviousness

"References relied upon to support a rejection under 35 USC 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). The prior art must provide one of ordinary skill in the art with the motivation to make the

proposed modifications needed to arrive at the claimed invention. *See In re Geiger* , 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. Here, the references do not teach one skilled in the art to select an antibody to a subunit of Stx2, in a therapeutically effective dosage, to treat or prevent HUS.

ii. The Claimed Invention

The claims define a formulation containing an effective dosage of antibodies reactive with a single subunit of Stx2, which neutralize Stx2, thereby preventing or treating hemolytic uremic syndrome ("HUS") in a human. The effective dosage for humans could be determined only using the neonatal pig model. See the example at pages 19-24. Absent this animal model, which is the only one predictive of human disease, one could not have determined an effective amount, the examiner's unsupported conclusions to the contrary. This is important to all of the claims on appeal, especially those defining a specific dosage, including claims 26 (effective amount), 31 (prevent neurological symptoms of HUS), 32 (prolong survival), and 34-36, which define actual dosages which were empirically determined to be effective.

The application demonstrates the efficacy of antibodies immunoreactive with a single subunit in preventing HUS associated mortality. Figures 2 and 3 demonstrate that applicants' humanized antibodies are neutralizing antibodies and their subunit specificity. Figures 4 and 6 show the average survival time of mice exposed to shiga like toxin II ("Stx2"), without treatment, and after treatment with humanized antibodies to subunit A of Stx2 (these results correlate with those in Figure 2, for antibody 5C12, which neutralizes Stx2 and Stx2A, and 6G3, which neutralizes Stx2 and Stx2A, showing that the antibody to the Stx2A is most effective). Sheoran, et al., "Tsx2-specific human monoclonal antibodies protect mice against lethal infection with *E. coli* expressing Stx2 variants" *Infect. Immun.* 71(6):3125-3130 (June 2003) was submitted as further evidence that the monoclonal antibodies to the individual subunits are protective, but that their activities are different depending on the specificity. As the data in the application and the paper demonstrates, the anti-Stx2 A antibodies have broader protection than the anti-Stx2 B antibodies. This is particularly relevant to claims 30 and 33, which are drawn to antibodies to specific subunits. Claims 30 and 33 are specific to particular subunits of the Shiga like toxin II. One could only determine the usefulness of the isolated subunits by actually making and then testing the antibodies to the subunits.

The prior art fails to teach any guidance as to (1) the selection of antibodies to Stx2 only to treat or prevent HUS, (2) that antibodies to a single subunit of Stx2 can be effective in preventing or treating disease (not just in a diagnostic assay) (as required by all of the claims on appeal) and (3) what constitutes an effective dosage of these antibodies (as defined functionally by claims 31 and 32, and by actual dosages by claims 34-36). It would not have been obvious from studies using animals such as mice what an

effective dosage would be, since mice are very resistant to infection, requiring many times more toxin to become sick, than humans. Only pigs have been proven to be a good model for humans (it is the only other animal species that naturally develops systemic complications when infected with Shiga toxin-producing *E. coli*), and therefore a model that allows determination of an effective dosage. Cattle cannot be used as animal models for human disease, since cattle do not contain the receptors on their blood vessels for the bacteria which infect humans, and therefore are not susceptible to the systemic disease as humans and piglets do. Therefore only studies conducted in pigs or humans can be used to determine the critical components of the disease causing etiological agent, what compounds would be effective to treat these critical components, and what the effective dosage of these compounds would be.

Moreover, the organisms isolated from cattle are antigenically distinct from the organisms isolated from humans. Even the terms are different. For example, the Shiga-like toxin II from *E. coli* infecting cattle is more similar to the Shiga-like toxin I of the *E. coli* infecting humans.

iii. The Prior Art:

Krivan

Krivan does not place one of skill in the art with antibodies to Stx2 which would be effective to treat or prevent ***human uremic syndome***. Krivan describes animal antibodies. It is not clear to what toxin - it appears that it is only to the SLT forms that cause animal disease, not to the Stx2 form causing HUS.

Perera does not teach antibodies for therapeutic use and suggests that antibodies to subunits of Stx2 are not as effective as antibodies to Stx1. An important aspect of the

studies conducted by Appellants was the use of a strain of bacteria which *infects and causes disease in humans.* Krivan does not recognize that the strains infect different hosts, and therefore that one cannot extrapolate from reagents in one species, cattle, for use in another, humans, even though the organism, *E. coli*, are the same, since there are differences in the toxins, and in the host species, cattle and humans which are infected differently and have different diseases.

Krivan teaches polyclonal, monospecific *bovine* antibodies for the detection of a Shiga-like toxin or for treating hemolytic uremic syndrome. There is no disclosure or suggestion in this reference to obtain a human monoclonal antibody that will bind to, and specifically neutralize, Stx2 from the *E. coli* in humans. Krivan does say one could treat humans - he does not say that one must use human antibodies, or antibodies to *E. coli* which infects and causes disease in humans. Indeed, Krivan does not even recognize that the bacteria that infect cattle are unable to infect humans and cause HUS. Therefore, Krivan does not disclose nor enable treatment of humans to prevent HUS.

Krivan says his antibodies and invention ***are not, and cannot be, useful in humans.*** As the following excerpt from the patent makes clear, the animals to be treated to make antibodies ***do not possess receptors for the toxin (thereby excluding humans), and the resulting antibodies therefore would not be administerable to humans (it is well known one cannot administer bovine antibodies by injection to humans):***

"To achieve the objects and accordance with the purpose of the invention, as embodied and broadly described herein, the present invention provides an antitoxin to one or more SLTs. It comprises purified IgG that contains high titer, monospecific polyclonal antibodies to a Shiga-like toxin. (col. 6, lines 17-21)

The antibodies can be purified from the IgG. Therefore, the invention also provides high titer, monospecific, purified polyclonal antibodies to an SLT. Preferably, the antibodies comprise bovine IgG." (col. 6, lines 22-26)

"As used herein, the term "Shiga-like toxin (SLT)" refers to any cytotoxin similar in both structure and function to Shiga toxin. Known SLTs include SLT-I, STX2, and STX2I. They also include known variants of STX2, which are STX2v, STX2vh, and STX2vp. The term encompasses the presently unknown SLTs or variants thereof that may be discovered in the future, since their characterization as an SLT or variant thereof will be readily determinable by persons skilled in the art." (col. 7, line 65 to col. 8, line 6)

"The purified IgG of the invention is made by a novel modification of standard techniques for making polyclonal antibodies by inoculating an animal with an antigen and recovering immunoglobulins from a fluid, such as serum, that contains the immunoglobulins after the animal has had an immune response. The inventors surprisingly and unexpectedly discovered that they were able to inoculate a bovine animal with a purified, preferably active, SLT without significant ill effect to the animal." (page 8, lines 7-15)

" Without wishing to be bound by theory, the inventors hypothesized that the cell membranes of the cells of such an animal do not contain a receptor for SLTs or only contain low levels of receptors, when compared to other mammals or humans. Presumably, this allows high amounts of purified, active toxin to be inoculated into the animal and presumably allows the toxin to remain in unbound form longer in the animal, thereby creating a much greater antigenic response." (col. 8, lines 16-24)

"***Therefore, the method of the invention is applied to any animal that has few or no receptors to SLTs. Such animals can be identified by those skilled in the art through standard techniques involving the injection of an SLT into the animal and the observation of its effect on the animal and the titer of antibodies produced by the animal.*** " (emphasis added) (col. 8, lines 25-30)

Accordingly, there is no teaching in Kriven of the need to make human or humanized antibodies to STX2, no teaching of how to make such antibodies, no recognition that this is the critical toxin to protect against, much less what an effective dosage is (as defined by claim 26), and even less so that one might target a specific subunit of the toxin as required by all of the claims, and specifically either subunit A (claim 30) or subunit B (claim 33). Polyclonal antibodies would not be specific to a single subunit ***unless one actively took the step of removing antibodies from the mixture which are reactive with the other subunit and the combination of subunits.***

Krivan teaches away from treating humans by stating that the method is for the treatment of animals that have few or no receptors to SLTs. Humans have receptors. That is why cattle and humans are different.

Williams

It is not clear that Williams is available as prior art, even under 35 U.S.C. 102(e), since it issued on an application filed March 13, 1997, well after appellants' priority date of November 15, 1996. Williams is drawn to the use of *avian* antibodies elicited by immunization of birds with recombinant, preferably cross-linked toxin fragments. These can allegedly be from subunit A or B of the toxin, which can be from a pathogenic strain of *E. coli*, including an *E. coli* which infects humans (col. 17). It is clear there is no

stated preference between stx1 and stx2 (col. 20, lines 38-45) although studies in mice showed protection from lethality *only* by using antibody to stx1, even though the antibody was a neutralizing antibody, (col. 66) which is the complete opposite to what appellant claims (antibodies to Stx2). From the discussion at col. 24, line 42 to col. 25, line 4, the patentees believed one can only obtain neutralizing antibodies by immunization to both subunits A and B, arranged in a conformationally correct manner, again the opposite of what is claimed, i.e, antibodies to a single subunit. Of course, their studies prove that just because an antibody is a neutralizing antibody, does not mean it protects from the toxin. There is no teaching or even recognition that one cannot inject avian antibodies into humans - see col. 27, line 62 to col. 28, line 44. The only immunization studies performed were in chickens and mice (col. 62-64), neither appropriate animal models for treatment or prevention of HUS. The only administration of antibodies was from rabbits into mice (example 19). However, the study was not done as it would occur in a natural state (oral infection) but by premixing toxin and antibody, then injecting it intraperitoneally into the mice. Col. 66. Therefore the results would not be predictive of efficacy in humans.

Perera

Perera is relied upon for its teaching of toxin neutralization. Perera teaches five monoclonal antibodies which bind to the -subunit of STX2 and were able to neutralize the toxin as assayed using HeLa cells or Vero cells *in vitro* (for example, see Materials and Methods, page 2128, 2 nd column). As noted at page 2130, col. 2, the antibodies are useful in diagnostics of disease. There is no mention of therapy other than to note that the shiga like toxins may play a role in disease "although no direct proof for the

involvement of SLTs in pathogenesis has yet been demonstrated." Perhaps more importantly, page 2131, col. 1, discusses the relative specificity and sensitivity of the antibodies, and notes that none of the antibodies reactive only with Stx2 could be used to detect organisms; antibodies to Stx2 which were effective were only able to be used to detect organisms producing both Stx1 and Stx2. Accordingly, one would not be led by Perera to use these antibodies in therapy, nor one would have a reasonable expectation of success using just an antibody to Stx2, much less to a single subunit of Stx2. The diagnostic results here clearly teach away from the use of the anti-Stx2 antibodies.

Perera even in combination with Krivan or Williams does not teach that these monoclonal antibodies alone would be effective in treating or preventing HUS, nor in what amount. There is not only no teaching of a therapeutic use, there is nothing that would lead one to estimate a dosage. Moreover, based on example 19 of Williams, the mere fact that an antibody is a neutralizing antibody (i.e., able to complex with antigen and neutralize charge so that a precipitate is formed) does not mean it will be therapeutically effective.

Queen and Engelman

Queen and Engelman were cited merely to show that humanized and/or recombinant antibodies could be made.

Queen generalizes as to the advantages of humanized antibodies over non-human antibodies. It should be noted that the advantages described therein, are generally directed to combinations of humanized light and heavy chains with donor immunoglobulin CDRs. These combinations are produced using recombinant genetic

and biochemical techniques. The techniques do not incorporate the use of an intact "immune system" to produce such humanized monoclonal antibodies.

iii. Appellants have submitted Expert Evidence which the examiner has ignored

Although appellants do not believe the examiner has established a *prima facie* case of obviousness, in view of the faulty analysis of the references, they have submitted expert evidence to rebut the examiner's rejection. The examiner keeps saying that because Krivan *claims* treatment of humans it enables and makes obvious treatment of humans, but this is contrary to the evidence submitted by appellants, which the examiner never rebuts with facts, only unsupported assertions. The declarations of experts in this field have been submitted that state that the foregoing analysis by appellants of the prior art is accurate and that Krivan neither discloses, nor makes obvious, such a formulation. The examiner has improperly ignored this evidence.

It has been well established that the examiner should consider all rebuttal arguments and evidence presented by applicants. Rebuttal evidence may include evidence of 'secondary considerations, such as 'commercial success, long felt but unsolved needs, [and] failure of others, evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art, or evidence that the claimed invention was copied by others. It may also include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. For example, rebuttal evidence may include a showing that the prior art fails to disclose or render obvious a method for making the compound, which would preclude a conclusion of obviousness of the compound. The examiner should not evaluate rebuttal evidence for its 'knockdown' value against the *prima facie* case or summarily dismiss it as not compelling or insufficient. If the evidence is deemed insufficient to rebut the prima facie

case of obviousness, the examiner should specifically set forth the facts and reasoning that justify this conclusion. In re Piasecki, 745 F.2d 1468 (Fed. Cir. 1984)

The evidence submitted by appellants is drawn to two areas: establishing the level of skill in the art and what the prior art teaches one of skill in the art. ... "[T]he point [is] that the legal conclusion of obviousness cannot be reached without an appreciation of the level of ordinary skill in the art, Graham v. John Deere Co. ... and that 'level' must be determined by a consideration of all evidence made available to the trier of the issue which is related to the state of the particular technology at a given point in time. When all the evidence is evaluated, it may well turn out and often does, that the level of skill was not quite what it appeared to be when only a portion of the evidence, e.g. printed patents or publications, was considered ... ."Most of the objective evidence presented by patent applicants to the Patent Office to establish non-obviousness, or, perhaps more correct in a procedural sense, to rebut a *prima facie* case of obviousness, is technical in nature--a comparison of the prior art products with the claimed products, for example. In re Palmer, 451 F.2d 1100, 172 USPQ 126 (CCPA 1971) "[T]his court ... has found patentable subject matter even where the invention is apparently simple in nature or quite 'close', on the surface, to the prior art, but where the small difference has eluded those of ordinary skill in the art in search of the solution to a persistent problem or where that difference unexpectedly yields an improved product or known product in an unexpectedly advantageous manner. *Id.*

The Declaration of Dr. Florian Gunzer:

Dr. Gunzer is a microbiologist in Germany, working on the virulence mechanisms of Shiga toxin producing *E. coli.* He has published in peer reviewed international

journals and is an Infectious Disease consultant with the department of pediatrics at the Hanover Medical School in Germany. He has been working on a swine model for human enteric infections since 1994. This is the swine model that was crucial for applicants' discoveries leading to the claimed formulations. He has recently verified that this model develops the same disease symptoms in humans including renal thrombotic microangiopathy, and concludes that it is unique in its potential for evaluating prophylactic or therapeutic approaches for HUS, including those factors critical for determining what an effective dosage and subunit specificity would be in humans.

The Declaration of Dr. John M. Leong

Dr. John M. Leong is an Associate Professor of Molecular Genetics and Microbiology at the University of Massachusetts Medical School, a former Pew Scholar in the Biomedical Sciences and a former Established Investigator of the American Heart Association. Dr. Leong states that there are two critical features leading to life-threatening complications by Shiga toxin producing strains of *E. coli* O157:H7: (1) secretion of shiga-like toxin, which is essential for the systemic manifestations of STEC infection, and (2) generation attaching and effacing (AE) lesions on the intestinal epithelium, lesions that disrupt the cytoskeleton of epithelial cells. He then also states that the only animal model for infections with *E. coli* O157:H7 and other serotypes of STEC is the neonatal gnotobiotic piglet. This is critical for one to determine an effective dosage and subunit specificity.

Declaration of Dr. Saul Tzipori

Dr. Tzipori is an inventor of this application. As he previously explained at the interview with the examiner, Dr. Tzipori spent two decades developing the pig model, to

determine the virulence factors of the *E. coli* that leads to hemolytic uremic syndrome (HUS). There are two important factors that only piglets and humans have: toxin receptors on blood vessels to produce disease symptoms such as kidney failure and brain damage by the absorbed toxin. The second key factor is the ability of the bacteria to cause attaching effacing (AE) lesions (damage to the gut wall) in pigs and in humans. This facilitates the absorption of the toxin from the severely damaged gut into the blood stream. Therefore only the piglets can be used as an animal model for this human disease. Moreover, only if the model has receptors on their blood vessels, and gut damaged by bacteria to facilitate absorption of the toxin, can one determine an effective dosage of the therapeutic. It is also critical for determination of subunit specificity.

Krivan does not describe a method of preventing HUS in humans. Krivan describes only the administration of polyclonal antibodies produced in cattle. These antibodies cannot be used to treat humans, nor is there any way to predict if they would be in the slightest way predictive of what could be done in humans. Appellants claim a composition of an effective amount of an antibody that is specific for a single subunit of Stx2 that can be administered by injection to a human to treat or prevent symptoms of HUS. Krivan's bovine antibodies cannot be administered to humans by injection since they would elicit an immune response. If one did administer them orally, the dosage would be very different from the dosage required for efficacy when administered by injection.

Dr. Tzipori attaches letters from two additional experts, Dr. Harley Moon of the College of Veterinary Medicine, Iowa State University, and Dr. Phillip I. Tarr, Professor of Pediatrics and Microbiology, Washington University School of Medicine in St. Louis,

that further demonstrate why the piglets are the only useful animal model and why such a model is critical to determine and characterize what an effective reagent is for treatment or prevention of HUS.

iv. The Prior art is not enabling nor does it provide the required motivation

As noted above, "References relied upon to support a rejection under 35 USC 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

Neither Krivan (bovine polyclonal antibodies) nor Williams (avian recombinant antibodies) places one of skill in the art with antibodies to STX2 which would be effective to treat or prevent HUS, and certainly not antibodies to a specific subunit of Stx2. None of the prior art teaches that one can treat or prevent symptoms in humans using an antibody to a single subunit of a single toxin, Stx2. Even if one skilled in the art were motivated to combine the teachings of Krivan and Williams, which is not provided by either, one would not have that which is claimed, nor could one possibly have any reasonable expectation of success. This could only come from having actual data from a suitable model for extrapolation to humans. This is critical with respect to the claims that

are drawn to the specific subunits, claims 30 and 33, to the claims for alleviation of specific symptoms, claims 31 and 32, and to the claims to defined dosages, claims 34-36.

Krivan only provides animal antibodies, and it is not clear to what toxin - it appears that it is only to the SLT forms that cause animal disease, not to the STX2 form binding to human receptors and thereby causing HUS in humans. William is focused on antibodies produced by immunization with a fusion peptide, and there is no evidence it could protect a human from developing symptoms Indeed, as noted above, Williams teaches one must have antibody to both subunits in order to have an efficacious antibody to any form of the bacteria in any species.

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Here, the examiner has taken the answer - that STX2 from certain enterohemorrhagic *E. coli* is critical to development of HUS in humans, and the data generated by Appellants with respect to the discovery that antibodies to specific subunits can be effective, to say that what is claimed is obvious. He ignores the necessity for actual data in a predictive animal model for one to be led to what is claimed with a reasonable expectation of success. As Appellants and all of the independent third party experts have testified, it was critical to have a useful animal model to make any

determinations: that antibodies to Stx2 alone could be used to treat or prevent symptoms of HUS; that antibodies to only a single subunit could be used to treat or prevent symptoms of HUS (and especially antibodies to subunit A, defined by claim 30, which was shown to be important in a number of strains in which antibodies to subunit B was not effective), and what would be effective dosages of such antibodies(defined by symptoms, claims 31 and 32, or amount, defined by claims 34-36). The examiner has worked backwards from Appellants' data to find references from which he has selected isolated phrases to support his rejection. This is clearly improper.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

As is clear from the expert Declarations, those skilled in the art believe one must have used an appropriate animal model to reach the claimed invention. Krivan in fact teaches away from this by teaching one should use an animal that does not have the receptors necessary for binding of the bacteria which causes disease in humans. The prior art must lead one to believe that antibodies to a single subunit of Stx2 could be

effective. The prior art does not do this, in any combination. Williams teaches away from such a composition by stating that the antibody should be made using a chimeric antigen of both subunits coupled together in a conformationally correct manner. The other references do not make up for these deficiences. Therefore the claimed methods cannot be obvious.

Moreover, as is very clear from the data in the application, that which is claimed achieves more than what would have been predicted. One could never have predicted that antibodies to subunit A (claim 30) would have efficacy against more strains than antibodies to only subunit B (claim 33) or the intact toxin.

The current rejections are analogous to the rejection deemed improper by the Federal Circuit. *See In re Deuel*, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). In *Deuel*, the Court reaffirmed that a rejection based on an "obvious to try" standard was improper. The Court specifically found that prior art that teaches a method for obtaining a general result, when the actual results are unknown, is insufficient to make obvious the actual results obtained upon which the claims are based.

One of ordinary skill in the art would readily appreciate neutralization of Stx2 *in vivo* is absolutely critical to prevent or treat hemolytic uremic syndrome in a human. The prior art never describes neutralization of the toxin that prevents death and other severe symptoms, as claimed. The prior art describes neutralizing antibodies only in the classic sense - antibodies which react with antigen to form an immunoprecipitate. The appellants have provided a detailed analysis of toxin induced neurological signs and bacterial lesions; and prevention and treatment of such signs and lesions in piglets. It is important to realize the advantages that are gained by using piglet model systems. Piglets

require much smaller toxin doses; piglets can be infected orally with the bacteria; mice are very resistant to infection, requiring many times more toxin to become sick, than humans; cattle do not absorb toxin at all like humans. In contrast, toxin produced in the gut of piglets is taken up systemically, ***just as in children***, to cause systemic complications because the piglets have receptors to which toxin binds. This information, provided only by Appellants, is critical to determining a dosage effective to treat or prevent the symptoms of claims 31 and 32 and to provide the dosage ranges of claims 34-36.

There is no teaching in the cited references, singly or in combination, of an effective dosage to prevent or treat hemolytic uremic syndrome in a human, especially of an antibody to Stx2, and even less so to a single subunit of Stx2. It would not have been obvious from studies using animals such as mice what an effective dosage would be, since mice are very resistant to infection, requiring many times more toxin to become sick, much less from studies with cattle. Studies based on preincubation and injection are worthless in predicting success, only failure. The bacterial strains and therefore the toxins, as well as the hosts and the diseases, are very different. One skilled in the art cannot predict from cattle, pig and avian diseases, to treatment or prevention of human infection. Accordingly, the claimed method cannot be obvious.

v. The examiner has failed to separately examine the dependent claims

The examiner has "lumped" all of the claims together in his rejections, and failed to separately examine the dependent claims. These can be divided into three groups, those defining the antibodies as recombinant or humanized or chimeric antibodies, those

relating to the formulation dosage, including claim 31 drawn to an effective amount to treat or prevent neurological symptoms, and those drawn to specific subunits, A or B (where A is shown to be significantly more effective than B), claims 30 and 33, as discussed above.

The prior art does not teach administration of humanized (claim 27), recombinant (claim 28) or chimeric humanized antibodies (claim 29). The examiner has used hindsight to say that it would be obvious to substitute humanized, recombinant or chimeric antibodies for the antibodies described by Krivan or Williams. This is not what one skilled in the art is led to by Krivan, however. Krivan teaches oral administration, not administration by injection, although he recognizes antibodies can be administered in other ways including injection. Krivan teaches the importance of polyclonal antibodies, not monoclonal antibodies. Krivan therefore fails to provide any teaching of why one would want to make a recombinant or humanized antibodies, much less how one should make such antibodies or use such antibodies. Williams describes polyclonal antibodies made to a recombinant antigen, not a recombinant or humanized antibody and says it would be useful to inject a human with avian antibody. Neither Krivan nor Williams indicate there is any need to do so. One cannot use hindsight to say that even though the prior art says it is desirable to use bovine or avian polyclonal antibodies for treatment, which can be administered enterally, one should replace them with humanized or human monoclonal antibodies to one particular toxin, Stx2, even less so to a single subunit of Stx2, which can be administered in defined dosages by injection to a human. This simply is found no where in the art.

The art also fails to suggest using an appropriate animal model that would lead one of skill in the art to determine an effective dosage. The art leads one instead to believe that mice and cattle are predictive of human treatment, and indeed Krivan teaches away from use of an animal with receptors as is essential in human infection. The expert opinions submitted by appellant make it very clear this not the case.

The dosage Krivan provides is for oral administration; not parenteral (col. 10, lines 54-55). This amount, 100 mg to 5 grams, greatly exceeds the amount that would be parenterally administered to a human child. There is no dosage given in Williams. None of the secondary references make up for the deficiencies of either Krivan or Williams.

One must look at the claims to see that very specific dosages are defined:

34. The dosage formulation of claim 26 equivalent to 4 ml serum from an animal immunized with Shiga-like toxin II/kg body weight.

35. The dosage formulation of claim 26 producing a serum level of anti-Shiga toxin II antibodies of at least 0.5 micrograms/ml.

36. The dosage formulation of claim 26 equivalent to a dosage of 3 mg human monoclonal antibody to Shiga-like toxin II administered to a newborn pig.

One must first start with the claim from which these claims depend - which requires the use of antibodies to treat humans, which are specific to a single subunit of Stx2. None of the art teaches anything with respect to whether or not the antibodies must react with one or both subunits of the toxin that is described. If one did decide to use an antibody to a single subunit, it is clear from the studies described in the application that one would have to determine experimentally which of the two subunits was more

important to prevention of disease or symptoms associated therewith. Then one would have to determine the effective dosage for these antibodies to the selected subunit.

The only way one skilled in the art could arrive at the claimed formulations is using hindsight based on appellant's studies; it is not derivable from the prior art. This is not something that could be predicted with any degree of certainty - it required experimental verification. Only appellants' data provides the information that could lead one to the claimed subject matter.

(9) SUMMARY AND CONCLUSION

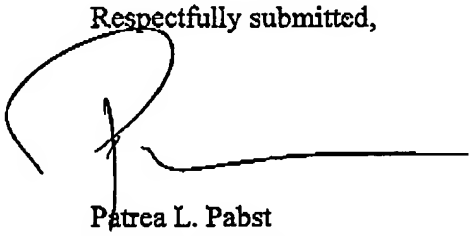
Krivan provides is a general teaching to treat or prevent disease in calves preferably administered orally, which is not suitable for injection into humans, and which is not specific to a particular subunit, nor in a dosage for administration by injection. Williams provides a recombinant peptide to immunize birds or rabbits. Williams teaches away from antibody to a single subunit by stating that it is very important to make antibody to an antigen consisting of two subunits coupled together to present the subunits in the same conformation as found in the native toxin (ie a conformation antigen).

The art does teach, nor lead one to, with a reasonable expectation of success, a formulation of antibodies to a single subunit of the Stx2 that causes HUS in humans, in a dosage that is effective to treat or prevent symptoms associated with debilitating disease or death. As the expert declarations demonstrate, those in the field did not know that one needed to target the shiga-like toxin II of the *E. coli* that infects humans, to prevent disease leading to death or kidney failure. This could not have been predicted based on data showing feeding of an immunoglobulin mixture to calves or pre-mixing toxin with

antibodies and injecting it intraperitoneally into mice. Neither calves nor mice are appropriate animal models for disease in humans since the disease proceeds differently due to the lack of receptors in the rumen of the calves, and the toxins are immunologically different. The only way one could have been led to the claimed subject matter is through extensive, careful, controlled studies conducted in a suitable animal model, as Appellants have done.

Based on the foregoing, claims 26-36 are not obvious in view of the cited art.

Respectfully submitted,



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APPENDIX OF CLAIMS ON APPEAL

26. (previously presented) A dosage formulation comprising an effective amount of human or humanized monoclonal antibodies, the antibodies consisting of antibodies neutralizing Shiga like toxin II *in vivo*, wherein the antibodies are specifically reactive with a single subunit of the Shiga like toxin II produced by *Escherichia coli* which causes hemolytic uremic syndrome, to prevent or treat hemolytic uremic syndrome in a human.

27. (previously presented) The dosage formulation of claim 26, wherein the antibodies are human monoclonal antibodies.

28. (previously presented) The dosage formulation of claim 26, wherein the antibodies are produced by recombinant DNA methodology.

29. (previously presented) The dosage formulation of claim 26, wherein the antibodies are chimeric monoclonal antibodies.

30. (previously presented) The dosage formulation of claim 26, wherein the antibodies bind to the alpha subunit of the Shiga like toxin II.

31. (previously presented) The dosage formulation of claim 26 wherein the antibodies are effective to prevent neurological signs of hemolytic uremic syndrome or lesions, wherein the neurological signs or lesions are selected from the group consisting of bloody diarrhea, acute renal failure, cerebral hemorrhaging, bacterial shedding into feces, bacterial lesions, paddling, head-pressing, ataxia, convulsions and wasting.

32. (previously presented) The dosage formulation of claim 26, wherein the antibodies are effective to prolong survival.

33. (previously presented) The dosage formulation of claim 26, wherein the antibodies bind to the beta subunit of the Shiga like toxin II.

34. (previously presented) The dosage formulation of claim 26 equivalent to 4 ml serum from an animal immunized with Shiga-like toxin II/kg body weight.

35. (previously presented) The dosage formulation of claim 26 producing a serum level of anti-Shiga toxin II antibodies of at least 0.5 micrograms/ml.

36. (previously presented) The dosage formulation of claim 26 equivalent to a dosage of 3 mg human monoclonal antibody to Shiga-like toxin II administered to a newborn pig.